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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/821,829 | MINOR, JAMES M. | |
| | Examiner | Art Unit | |
| | KARLHEINZ R. SKOWRONEK | 1631 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *25 January 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-13,17-20 and 35-42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13, 17-20, and 35-4* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Claim Status*

Claims 1-13, 17-20, and 35-42 are pending.

Claims 14-16 and21-34 are cancelled.

Clams 35-42 are new.

Claims 1-13, 17-20, and 35-42 are being examined.

### *Claim Rejections - 35 USC § 101*

### *Response to Arguments*

Applicant's arguments, see Remarks p. 8, filed 25 January 2008, with respect to the rejection of claim 17 as being directed to non-statutory subject matter under 35 USC 101 have been fully considered and are persuasive. The rejection of claim 17 has been withdrawn in view of the amend to the claim.

The following rejection is reiterated from the previous action.

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-13, 17-18, and 39-42 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claims 1-13, 17-18, and 39-42 are drawn to a process. A statutory process must include a step of a physical transformation, or produce a useful, concrete, and tangible result (State Street Bank & Trust Co. v. Signature Financial Group Inc. CAFC 47 USPQ2d 1596 (1998), AT&T Corp. v. Excel Communications Inc. (CAFC 50 USPQ2d

1447 (1999)). The instant claims do not result in a physical transformation, thus the Examiner must determine if the instant claims include a useful, concrete, and tangible result.

As noted in State Street Bank & Trust Co. v. Signature Financial Group Inc. CAFC 47 USPQ2d 1596 (1998) below, the statutory category of the claimed subject matter is not relevant to a determination of whether the claimed subject matter produces a useful, concrete, and tangible result:

> The question of whether a claim encompasses statutory subject matter should not focus on which of the four categories of subject matter a claim is directed to -- process, machine, manufacture, or composition of matter--but rather on the essential characteristics of the subject matter, in particular, its practical utility. Section 101 specifies that statutory subject matter must also satisfy the other "conditions and requirements" of Title 35, including novelty, nonobviousness, and adequacy of disclosure and notice. See *In re Warmerdam*, 33 F.3d 1354, 1359, 31 USPQ2d 1754, 1757-58 (Fed. Cir. 1994). For purpose of our analysis, as noted above, claim 1 is directed to a machine programmed with the Hub and Spoke software and admittedly produces a "useful, concrete, and tangible result." *Alappat*, 33 F.3d at 1544, 31 USPQ2d at 1557. This renders it statutory subject matter, even if the useful result is expressed in numbers, such as price, profit, percentage, cost, or loss.

In determining if the claimed subject matter produces a useful, concrete, and tangible result, the Examiner must determine each standard individually. For a claim to be "useful," the claim must produce a result that is specific, and substantial. For a claim to be "concrete," the process must have a result that is reproducible. For a claim to be "tangible," the process must produce a real world result. Furthermore, the claim must be limited only to statutory embodiments.

Claims 1-13, 17-18, and 39-42 do not require the production of a tangible result in a form that is useful to the user of the process or apparatus. A tangible result requires that the claim must set forth a practical application to produce a real-world result. This rejection could be overcome by amendment of the claims to recite that a result of the process is outputted to a display, or to a user, or in a graphical format, or in a user

readable format, or by including a result, that is a physical transformation. The applicants are cautioned against introduction of new matter in an amendment.

***Response to Arguments***

Applicant's arguments filed 25 January 2008 have been fully considered but they are not persuasive. Applicant argues claims 1-13 and 17-18 were not explicitly rejected. Applicant's statement that the claims were not "explicitly" rejected is interpreted to mean that applicant also interpreted the discussion of claims 1-13 and 17-18 under 35 USC 101 as a rejection of the claims, albeit an implicit rejection. To eliminate any confusion, the rejection has been modified to explicitly point out that claims 1-13 and 17-18 are rejected under 35 USC 101.

Applicant argues claims 1-13 and 17-18 are not directed to a judicial exception because the claims are not drawn to a law of nature, natural phenomena, or abstract idea. This is argument is not persuasive. Despite applicant's assertion, the claims are directed to an abstract idea. The claims are directed to an abstract method of rank ordering characteristics of properties. In the method a plurality of characteristic signatures are formed based on data obtained from measurements obtained from tissues samples. Tissue samples do not naturally possess characteristic signatures, rather characteristic signatures are an abstract idea developed to create and describe a artificial distinction between the tissue samples in the mind of man. The method further applies the steps of providing a trend profile, performing statistical analysis of the characteristic signatures with regard to the trend profile, and rank ordering the characteristic signatures. These steps of the method are also directed to an abstract

idea, namely abstract mathematic algorithms for statistics, rank ordering and profile generation. Therefore, taking the claim as a whole, the subject matter of the claim is directed to an abstract idea which is an algorithm for mathematically manipulating data measured from tissue samples. The method does not result in the transformation of physical object in to a different state or thing. The claims do not result in a physical transformation nor do they produce a tangible result, and are thus not statutory.

Applicant argues that the claims results in a real world result in producing rank ordered characteristics signatures. This argument is not persuasive. If a rank ordered characteristic signature were returned to the practitioner of the method for producing rank ordered characteristic signatures, then the method would have produced a real world result. In the instant case, no such result is returned to the practitioner of the instantly claimed method. Thus, the method does not produce a real world result.

Applicant argues that the claimed process produces a physical transformation as far as claims 2-4 and 12 are concerned. However, in the process of interpreting the claims as a whole, the instant claims are directed to the mathematical manipulation of data. In this case, the claims are directed to producing result for an abstract mathematical manipulation. Claims 2-4 and 12 are merely directed to identifying more directly the source of data used in the mathematical manipulation. The rejection is maintained.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 17 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

What is claimed: A computer readable medium carrying one or more sequences of instructions for rank ordering characteristic signatures of properties where the computer readable medium is not a carrier wave or signal *per se* is claimed. The claim is interpreted to be directed to any computer readable that is not a carrier wave or signal *per se*.

What the specification teaches: The specification shows at page 25 to page 26, paragraph 77, that computer readable media may be of the kind well known and available to those having skill in the art. The specification gives some examples of computer readable media, also at p.26, paragraph 77. The definition of computer readable media presented by applicant is broad and non-limiting. The specification does not show that computer readable media were contemplated by applicant to specifically exclude carrier waves or signals *per se*.

What is reduced to practice: The disclosure doe not show the reduction to practice of a computer readable medium carrying one or more sequences of instructions for rank ordering characteristic signatures of properties. The specification does reduce to practice the generation of T-CURVEs from gene expression data.

What the drawings show: Figure 10 shows a computer system having an CD-ROM input source at least one processor and an input/output to a network connection from the processor.

A showing of sufficient relevant identifying characteristics: The specification shows various computer readable media with sufficient relevant identifying characteristics. The specification teaches examples of computer media are not limited magnetic media such as hard disks, floppy disks, and magnetic tape; optical media such as CD-ROM, CDRW, DVD-ROM, or DVD-RW disks; magneto-optical media such as floppy disks, and hardware devices that are specially configured to store and perform program instructions, such as read-only memory devices (ROM) and random access memory (RAM) at page 25, last line to p. 26, line 5. However, the specification does not show that computer readable media are not carrier waves or signals *per se* with sufficient relevant identifying characteristics.

Method of making the claimed invention: The specification shows at p.25, paragraph 77 that computer readable media are well known in the art.

Level of skill and knowledge in the art: Computer-readable media are also known in the art as machine-readable media. The academic press dictionary of science and technology defines machine-readable portion of the term machine-readable storage media as "Describing any printed material or storage medium that can be automatically read by a computer, especially a medium that is not normally readable..." (Machine-readable, 1992, In Academic Press Dictionary of Science and Technology. Retrieved April 27, 2008, from www.credoreference.com/entry/3177150). Kartaschoff

(Proceedings of the IEEE, vol. 79, No. 7, p. 1019-1028, July 1991) shows that three main categories of machine-readable transmission media exist, metallic wire, optical fiber and radio transmission (p. 1020, col.1). The level of skill and knowledge in the computer science art is high.

Predictability in the art: The use of carrier signals and waves in the art as a machine-readable media is predictable.

Conclusion: While one of ordinary skill would have been able to use carrier waves or signals as computer readable media, the disclosure doe not support the specific exclusion of carrier waves and signals as a computer-readable medium. Therefore, claim 17 as currently claimed, directed to a computer readable medium that is not a carrier wave or signal *per se*, is new matter and lacks written description in the disclosure as originally filed.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 1-13, 35, and 37 are rejected under 35 U.S.C. 102(b) as being anticipated by Singh et al. ("Gene Expression Correlates Of Clinical Prostate Cancer Behavior", Cancer Cell, Vol.1, March 2002) as evidenced by Singh et al. supplemental (Singh et al., [online], www.cancer cell.org/cgi/content/full/1/2/203/DC1, 2002).

The claims are drawn to a method for rank ordering characteristic signatures of cell properties, said method comprising the steps of: forming a plurality of characteristic signatures for a plurality of cell properties having been measured from a plurality of samples taken from a heterogeneous tissue region, wherein the heterogeneous tissue region includes a first portion having at least first and second types of tissue, bordered by a second portion, said second portion considered to be devoid of the second type of tissue, wherein the plurality of samples have been taken from successive locations along a determined profile of locations through the heterogeneous tissue region, with at least one sample being taken from the second portion, and wherein each of said characteristic signatures characterizing one of the plurality of properties, respectively; providing a trend profile of cell activity for the second type of tissue along the determined profile of locations through the heterogeneous tissue region; performing statistical analysis on each of the plurality of characteristic signatures with regard to the provided trend profile; and rank ordering the plurality of characteristic signatures based on proximity to the trend profile as determined by the statistical analysis.

Singh et al. teach a method for rank ordering characteristic signatures of cell properties. To summarize the teaching, Singh et al. have taken normal prostate tissue that is bordered on two sides by diseased tissue and performed gene expression analysis and histological examinations of the samples resulting in a rank ordering of characteristic genes that can be used in the early diagnosis of prostate cancer.

Singh et al. takes a plurality of samples from the prostates of patients undergoing radical prostatectomy. The prostate of each patient is viewed as a heterogeneous tissue

region composed of two portions. The first portion is composed of blood vessels and diseased tissue (Tumor) and the second portion is devoid of diseased tissue (Normal) (first paragraph, Tumor vs. normal classification, p.204). Singh et al shows that for each prostate of each patient a pair of samples was taken one tumor and one normal (Singh et al supplemental p. 2). Based on a known trend for tumorous prostate to have a higher Gleason Score than normal or healthy prostate (introduction, second paragraph, p. 203), Singh et al. performed histological examinations on a plurality of samples taken across the tissue to identify a characteristic signature Gleason score profile (3rd paragraph, Discussion, p.206). The gene models, provided in 4 and 16 gene models, of Signh et al. provided a trend profile of cell activity for the second type (diseased) of tissue along the profile of locations in the tissue (p 204, col. 1-2). The samples were also used to perform gene expression analysis. Resulting from the gene expression analysis was a rank ordering of signature genes (2nd paragraph, Results: Tumor vs. Normal classification, p. 204). In the instant case, a plurality of cell properties is interpreted to include the individual expression states of a plurality of genes, i.e. a cell property can be the expression state of a particular gene, and thus a characteristic signature is a particular profile of expression for a gene or subset of genes in the context of a particular cell or tissue type. In the course of their gene expression analysis, Singh et al. formed a plurality of characteristic signatures from a plurality of cell properties (paragraph 2, Results: Prediction of Pathological features of Prostate Cancer, p. 204). Singh et al. performed statistical analysis on each of the plurality of characteristics signatures with regard to the provided trend profile. The statistical

analysis was in the form of a correlation between the expression of particular genes and the Gleason score (Prediction of Pathological Features Of Prostate Cancer, p. 204). Singh et al. used two-step ranking procedure. In the first step, genes were ranked based on their expression relative to the tissue type (normal vs. diseased). In the second step, genes were ranked based on their correlation with the Gleason score to result in a "hierarchical clustering", interpreted as ranking (second paragraph, Prediction of Pathological Features Of Prostate Cancer, p. 204). Singh et al. further illustrate the rank ordering of a plurality of characteristic signatures in figure 3 (p. 207).

Regarding claim 2, Singh et al. teach the step of measuring the plurality of cell properties for each of the plurality of samples. Singh et al. measured among others prostate serum antigen Gleason score, seminal vesicle invasion, gene expression, and pathological stage (Table 1, p. 205 and fig 1, p. 206).

Regarding claim 3, Singh et al. teach the steps of: providing the heterogeneous tissue region: and taking the plurality of samples from the heterogeneous tissue region, "...samples of prostate tumors and adjacent prostate tissues not containing tumor...were collected" (Prostate tissue samples, p. 208) (see also figure 1 of this office action).

Regarding claim 4, Singh et al. teach the step of: measuring the plurality of cell properties for each of the plurality of samples (Gene expression measurements, p. 208). "High-quality expression profiles were successfully derived ... using oligonucleotide microarrays containing probes for approximately 12,600 genes..."(Results, Tumor vs. Normal classification, first paragraph, p. 204).

Regarding claim 5, normalizing with respect to baseline established using healthy tissue, Singh et al. teach 317 genes had higher expression in tumor samples (Results: Tumor vs. Normal classification, second paragraph, p. 204).

Regarding claim 6, Singh et al. teach the step of performing statistical analysis includes: comparing each of the plurality of characteristic signatures with the provided trend profile by curve-fitting to a statistical regression function, wherein said curve-fitting determines the degree of proximity of each of the plurality of characteristic signatures to the provided trend profile ("K-nearest neighbor (k-NN) class prediction models", p. 208).

Regarding claim 7, Singh et al. teach the step of performing statistical analysis includes: calculating a p-value with regard to each of the plurality of characteristic signatures, to test the null hypothesis between each of the plurality of characteristic signatures and the provided trend profile ("P-values", Experimental Procedures, in Correlation Of Gene Expression With Continuous Variables, p. 208; and in Gene Ranking, Class Prediction By *K*-Nearest Neighbors And Permutation Testing For Dichotomous Variables, p. 208).

Regarding claim 8, the statistical analysis is done in one two or three-dimensional space, Singh et al. teach the S2N statistical technique.

Regarding claim 9, Singh et al. teach the first type of tissue is healthy tissue (Experimental Procedure, Prostate Tissue Samples, p. 208).

Regarding claim 10 and 37, Singh et al. teach the second type of tissue is diseased tissue (Experimental Procedure, Prostate Tissue Samples, p. 208).

Regarding claim 11, Singh et al. teach one of the plurality of properties is an expression level of a gene (gene expression measurements, p. 208).

Regarding claim 12, Singh et al. teach the step of measuring a plurality of properties includes: processing each of the plurality of samples using a microarray technique (gene expression measurements, p. 208).

Regarding claim 13, the step of measuring a plurality of properties includes: processing each of the plurality of samples on a single two-color microarray, two single-color microarrays or both is inherent to the teaching of Singh et al. It is understood in the art that the application of microarrays to measure gene expression requires the use of minimally, 1 labeled sample and more commonly involves the use of 2 differentially labeled sets of probes thus the number of colors used in a microarray experiment is an intrinsic property of the microarray.

Regarding claim 35, Singh et al. show that results are returned to a user (table 1 and figure 1).

***Response to Arguments***

Applicant's arguments filed 25 January 2008 have been fully considered but they are not persuasive.

Regarding the rejection of claims 1-13 under 102(b) over Singh et al, Applicant argues that the prior art fails to teach the limitation of a plurality of characteristic signatures from measurements taken from samples taken from successive locations along a determined profile of locations through the heterogeneous tissue.

Singh et al. teaches taking a plurality of samples from the prostates of patients undergoing radical prostatectomy (208, col. 1, prostate tissue samples, line 1-3). Prostatectomy is the removal of the heterogeneous tissue known as the prostate that is composed of a plurality of tissue types of a t least a first tissue type, for example blood vessels, muscle, epithelial, or nerve. Singh et al. shows that of 253, 65 prostate specimens were determined to have tumor on opposing sides of the specimen and 52 were used for the analysis (204, col. 1, results tumor vs normal classification, line 5-6, p208, col. 1, Prostate tissue samples, lines 4-5). Singh et al shows that for each prostate of each patient a pair of samples was taken one tumor and one normal. Further, regarding the prostate tissue samples used by Singh et al., Singh et al. shows in the Experimental procedures section at p. 208, col. 1, "Prostate tissue samples", para. 1, line 1-5, that "From 1995 to 1997 samples of prostate tumors and adjacent prostate tissue not containing tumor (referred to as 'normal') were collected from patients undergoing radical prostatectomy at the Brigham and Women's Hospital. From 235 'tumor' samples, 65 had cancer present on opposing sides of the OCT embedded specimens".

Thus giving the claims their broadest reasonable interpretation, the teaching of Singh et al. taking two samples, one of normal tissue and one of diseased tissue, from each of the 52 prostates obtained teach the limitations of the claims reciting a "plurality of samples from". The claims do not require a plurality of samples be taken from the first portion. The claim only requires that a plurality of samples be taken from the tissue region. The samples of Singh et al satisfy the limitation. The claim also requires that the

samples be taken from predetermined location of the tissue region. Singh et al also satisfies that limitation. Finally, the claim only requires that at least one sample be taken from a portion of the tissue region devoid of the second type of tissue. The normal samples of Singh et al satisfy that limitation as well because the samples are devoid of tumor.

Singh et al. teach obtaining gene expression profiles from tumor and normal tissue samples using microarrays of 12,000 genes (p. 204, col. 1, results tumor vs normal classification, line 6-11). The 12,000 genes on the array are viewed to read on the plurality of properties recited in the claims. The gene expression recited by Singh et al. reads on the characteristic signature as instantly claimed. Singh et al. make correlation between Gleason score (GS) and the measured gene expression profiles. Teaching specifically, that a readily detectable and statistically significant signature of GS exists (p. 206, col. 1, para. 2, line 7-9). Singh et al. also teach gene expression signature profile composed of a plurality of gene expression signatures of GS (p. 204, col. 2 para. 2, lines 1-5). Singh et al. provide a trend profile for the second type of tissue and perform a statistical analysis on each of the characteristics signatures First, Singh at al. teach profile of a second tissue determined along the profile of locations in providing a "normal" gene expression profile (p. 204, col. 1, results tumor vs normal classification, lines 8-10). Second, the statistical comparison between the particular gene measures in normal versus tumor tissue (p. 204, col. 1, results tumor vs normal classification, para 2, line 3-7). Third, Singh et al. teach ranking the profile signatures (p.

204, col. 1, results tumor vs normal classification, para 2, line 1-3). Thus providing rank ordered characteristic signatures as in claim 1.

Applicant also argues that the expression profiles of Singh et al. are not anticipatory of the instantly claimed characteristic signatures. This is not found persuasive. The specification does not explicitly define "characteristic signatures". The specification recites, "characteristic signatures characterize one of the plurality of properties" and characteristic signatures are formed using the measured plurality of properties" (specification, [0006] line 7-8). A gene is interpreted to be a property and gene expression is interpreted to be a characteristic signature. Based on the guidance provided by the specification, Singh et al. teaches obtaining gene expression data (characteristic signatures) from normal and tumorous samples for 12,000 genes (properties). The samples in Singh et al. are taken from predetermined locations in the prostate specimen because the samples were taken from regions in the specimens that were tumorous and non-tumorous. Further, with regard to the argument that Singh et al. fails to disclose a plurality of characteristic signatures from samples taken from successive locations along a determined profile of locations through the heterogeneous tissue region. Based on the description of the specimen used in the study performed by Singh et al., Singh et al. shows that a plurality of samples is taken from the heterogeneous tissue region. Specifically, Singh et al. shows that 2 samples, a plurality of samples, were taken from each of 50 heterogeneous tissues specimens composed of tumor tissue and normal tissue. Singh et al. shows that each of the samples was used to determine gene expression for a plurality of genes. Thus, Singh et al. shows a

plurality of characteristic signatures from samples taken from successive locations along a determined profile of locations through the heterogeneous tissue region. Applicant argues that the instant invention is further distinguished from Singh et al. because the instant invention takes samples from successive locations of the same heterogeneous tissue region. Analogous to the instant invention, Singh et al. takes samples from two successive locations from the same prostate specimen.

Applicant argues that Singh et al. fails to show a heterogeneous tissue region. The argument is not persuasive as is addressed in detail above.

Thus the rejection of claims 1-13 as anticipated by Singh et al. under 35 USC 102(b) is maintained.

The following rejection is maintained from the previous office action and amended as necessitated by amendment.

Claims 1-10, 12-13, 17-20, and 35-39 are rejected under 35 U.S.C. 102(e) as being anticipated by Crosby et al. (US PG Pub 2003/0190689).

The claims are drawn to a method for rank ordering characteristic signatures of cell properties, said method comprising the steps of: forming a plurality of characteristic signatures for a plurality of cell properties having been measured from a plurality of samples taken from a heterogeneous tissue region, wherein the heterogeneous tissue region includes a first portion having at least first and second types of tissue, bordered by a second portion, said second portion considered to be devoid of the second type of tissue, wherein the plurality of samples have been taken from successive locations

along a determined profile of locations through the heterogeneous tissue region, with at least one sample being taken from the second portion, and wherein each of said characteristic signatures characterizing one of the plurality of properties, respectively; providing a trend profile of cell activity for the second type of tissue along the determined profile of locations through the heterogeneous tissue region; performing statistical analysis on each of the plurality of characteristic signatures with regard to the provided trend profile; and rank ordering the plurality of characteristic signatures based on proximity to the trend profile as determined by the statistical analysis. In some embodiments, the results are output to a user in a user readable format.

Cosby et al. teach method of identification of the most relevant biomarkers of disease progression. In their method, Crosby et al. form a plurality of characteristic signatures of plurality of cell properties measured from a plurality of samples taken from a heterogeneous tissue region. In Crosby et al. the plurality of samples is from a heterogeneous tissue region are in the form of multiple sequential tissue slices ("cellular assays...", [0080], p. 9). The sequential tissue slices are cross-sectional tissue samples analogous to the sampling points 108a-n exemplified in figure 1 of the instant application. Crosby et al. analyze the cells that compose the sequential tissue slices by immunohistochemistry (IHC) using antibodies recognizing the phosphorylation state of signal transduction proteins ("...phospho-specific antibodies...", [0025], p. 3 and [0081], p. 9). Crosby et al. disclose samples having negative and positive disease outcomes ("...samples from patients having negative...", [0025], p. 3) is viewed to read on heterogeneous tissue region including a first portion having at least a first and second

types of tissue, bordered by a second portion considered to be devoid of the second type of tissue. Tissue that has a negative disease outcome is normal, whereas tissue that has a positive disease outcome is diseased. Crosby et al. provide a trend profile of cell activity for the second type of tissue by hypothesizing the disease involves altered signal transduction ("...down stream pathway markers...", [0008], p. 1 and "...altered signal transduction", [0025], p. 3). Crosby et al. perform statistical analysis on each of the plurality of characteristic signatures with regard to the trend profile by establishing a "significant correlation" based on the statistically difference between a characteristic signature compared to an outcome than to random chance ("significant correlation", [0043], p. 5). In Crosby et al., the characteristic signatures are rank ordered based on proximity of to the trend profile as determined by the statistical analysis using statistical clustering techniques to identify the best (highest rank) characteristic signature associated with disease outcome ("Such correlation analysis...", [0094], p. 9).

Regarding claims 2 and 4, Crosby et al. measure the plurality of cell properties for each of the plurality of samples through the use of a plurality phospho-specific antibodies to detect the phosphorylation statuses of a plurality of signal transduction proteins ("Such panels...", [0060], p. 6).

Regarding claim 3, providing the heterogeneous tissue region and taking a plurality of samples, Crosby et al. teach obtaining cellular samples from a plurality of patients ("...obtaining...", [0025], p. 3).

Regarding claim 5, normalizing the characteristic signature to a baseline, Crosby et al. teach altered activity (relative to the non-diseased state) ([0033], p. 4 and claim 26, step c).

Regarding claim 6 and 7, comparing each of the plurality of characteristic signatures with the trend profile and calculating a p-value, Crosby et al. teach the chi-squared statistical test ("Chi-squared tests" and "P-value", [0043], p. 5).

Regarding claim 8, the statistical analysis is done in one two or three-dimensional space, Crosby et al. teach the Chi squared test as noted above and a multi dimensional plot in figure 3a that is based on the cluster analysis statistical technique.

Regarding claim 9, 10 and 37-39, the first type of tissue is healthy tissue and the second type of tissue is diseased tissue, Crosby et al. teach the samples from patients having negative and positive disease outcomes, which is viewed as the first type of tissue is healthy tissue and the second type of tissue is diseased tissue. Tissue that has a negative disease outcome is healthy (non-diseased), whereas tissue that has a positive disease outcome is diseased ("...samples from patients having negative...", [0025], p. 3).

Regarding claim 12, processing the plurality of samples using a microarray technique, Crosby et al. teach the application of a tissue microarray ("tissue microarray", [0078], p. 8).

Regarding claim 13, a single two-color microarray or two single-color microarrays or both. Since in a tissue microarray the tissue samples are bound to a solid support, a

plurality of probes (antibodies in the case of Crosby et al.) labeled with a plurality of chromophores can be used to detect the presence of the target.

Regarding claim 17 and 18-20, a computer readable medium carrying instructions or a system for performing rank ordering by the steps of forming a plurality of signatures, providing a trend profile performing statistical analysis and rank ordering, Crosby et al. teach the automated analysis of stained tissues or cells ("Scoring" and "automatic cell staining instruments", [0077], p. 8 and "...using statistical software...", [0091], p. 9). The implementation of microprocessors is an inherent property of any automated system in biotechnology; accordingly, necessary to the particular automated system is a computer readable medium to provide the instructions to the microprocessor. The computer readable medium could be, for example, magnetic disk, optical disk, or IC chip. With regard to the limitations of claim 17 of a computer readable medium and 18 a system, Crosby et al. teach automatic analysis using high-throughput automation [0013].

Regarding claims 35 and 36, Crosby et al. shows the results are output to a user ([0094] and figures 2 and 3).

***Response to Arguments***

Applicant's arguments filed 25 January 2008 have been fully considered but they are not persuasive.

Regarding the rejection of claims 1-10, 12-13 and 17-20 as anticipated by Crosby et al. under 35USC102(e).

Applicant argues that Crosby et al. does not teach the limitations of the independent claims 1, 17, and 18. This is not found persuasive.

Applicant argues, specifically, that Crosby et al. fails to suggest the sampling of multiple locations along a profile in a tissue. The argument is not found persuasive because Crosby et al. shows the rapid analysis of multiple sequential tissue slices in parallel by IHC reading on the limitation of multiple samples along a determined location profile ([0023], p. 3, col 2). Crosby et al. continues at [0023] to show using ImmunoHistoChemsitry (IHC), particular cells having activated proteins can be identified and be directly compared to normal cells, reading on a heterogeneous tissue region having first and second types of tissue. Crosby et al. further show obtaining a plurality of samples from patients having positive and negative disease outcomes [0025] reading on the plurality of samples. Crosby then detects the phosphorylation statuses of a plurality of signaling proteins [0025] reading on forming a plurality of characteristics. Reading on the limitation of measuring from a plurality of samples take from a heterogeneous tissue region, Crosby et al. teach the analysis of multiple sequential tissue slices [0080]. Crosby et al. teach determining the correlation of protein activity (characteristic signature) and a disease outcome (trend profile)[0092] and identification of the best (most highly correlated, i.e. rank ordered) biomarkers [0094] reading on providing a trend profile, performing a statistical analysis on each of the characteristic signatures with regard to the trend profile, and rank ordering the characteristic signatures.

Thus the rejection of claims 1-10, 12-13 and 17-20 as anticipated by Crosby et al. under 35USC102(e) is maintained.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 17-18, and 37-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Crosby et al. in view of Rubin et al. (Am. J. Surg. Pathol, Vol. 26, No. 3, p. 312-319, 2002) and in view of Liotta et al. (Nature reviews: Genetics, Vol. 1, p. 48-56, October 2002).

The claims are directed to a method, computer readable medium, and system for rank ordering characteristic signatures of cell properties, said method comprising the steps of: forming a plurality of characteristic signatures for a plurality of cell properties having been measured from a plurality of samples taken from a heterogeneous tissue region, wherein the heterogeneous tissue region includes a first portion having at least first and second types of tissue, bordered by a second portion, said second portion considered to be devoid of the second type of tissue, wherein the plurality of samples have been taken from successive locations along a determined profile of locations through the heterogeneous tissue region, with at least one sample being taken from the second portion, and wherein each of said characteristic signatures characterizing one of the plurality of properties, respectively; providing a trend profile of cell activity for the second type of tissue along the determined profile of locations through the heterogeneous tissue region; performing statistical analysis on each of the plurality of characteristic signatures with regard to the provided trend profile; and rank ordering the plurality of characteristic signatures based on proximity to the trend profile as determined by the statistical analysis. In some embodiments, the second type of tissue comprises disease tissue. In some embodiments, a plurality of samples are taken from the first portion.

Cosby et al. teach method of identification of the most relevant biomarkers of disease progression. In their method, Crosby et al. form a plurality of characteristic signatures of plurality of cell properties measured from a plurality of samples taken from a heterogeneous tissue region. In Crosby et al. the plurality of samples is from a heterogeneous tissue region are in the form of multiple sequential tissue slices ("cellular assays…", [0080], p. 9). The sequential tissue slices are cross-sectional tissue samples analogous to the sampling points 108a-n exemplified in figure 1 of the instant application. Crosby et al. analyze the cells that compose the sequential tissue slices by immunohistochemistry (IHC) using antibodies recognizing the phosphorylation state of signal transduction proteins ("…phospho-specific antibodies…", [0025], p. 3 and [0081], p. 9). Crosby et al. disclose samples having negative and positive disease outcomes ("…samples from patients having negative...", [0025], p. 3) is viewed to read on heterogeneous tissue region including a first portion having at least a first and second types of tissue, bordered by a second portion considered to be devoid of the second type of tissue. Tissue that has a negative disease outcome is normal, whereas tissue that has a positive disease outcome is diseased. Crosby et al. provide a trend profile of cell activity for the second type of tissue by hypothesizing the disease involves altered signal transduction ("…down stream pathway markers…", [0008], p. 1 and "…altered signal transduction", [0025], p. 3). Crosby et al. perform statistical analysis on each of the plurality of characteristic signatures with regard to the trend profile by establishing a "significant correlation" based on the statistically difference between a characteristic signature compared to an outcome than to random chance ("significant correlation",

[0043], p. 5). In Crosby et al., the characteristic signatures are rank ordered based on proximity of to the trend profile as determined by the statistical analysis using statistical clustering techniques to identify the best (highest rank) characteristic signature associated with disease outcome ("Such correlation analysis…", [0094], p. 9).

Crosby et al. do not show that a plurality of samples is taken from the first portion.

Rubin et al. shows that a plurality of samples is taken from a heterogeneous tissue region (figure 1). Rubin et al. shows an advantage of taking a plurality of samples from the first portion is that a plurality of samples increases the accuracy of the information gained from the sampling (p. 312, col. 2, abstract).

Liotta et al. shows that the molecular analysis of cells in their native tissue environment provides the most accurate picture of the *in vivo* disease state (p. 49, col. 2). Liotta et al. shows that the analysis of cells in their native tissue environment is complicated by the fact that a particular cell population of interest may constitute a tiny fraction of the total tissue population (p. 312, col. 2). In other words, the analysis of cells in their native tissue environment is complicated because tissues are heterogeneous. Liotta et al. illustrates in figure 1 the heterogeneous nature of tissues and its effect on the outcome of profiling. Liotta et al. shows that specific cell populations can be isolated from "contaminating" cellular subpopulations by microdissection (p. 313, col. 2). Liotta shows that micro dissection is easy and rapid (Box 2).

It would have been obvious to one of ordinary skill in the art to modify the method Crosby et al. with the plurality of sample from the first portion of Rubin et al. because

Rubin et al. successfully shows that a plurality of samples increases the accuracy of the information gained from the sampling which is an advantage. It would have been further obvious to one of ordinary skill in the art to modify the method Crosby et al. in view of the plurality of sample from the first portion of Rubin et al. with the use of heterogeneous tissues and the analysis of specific cellular populations isolated from contaminating sub-populations because Liotta et al. shows the separation yields a profile targeted to the specifically chosen population.

Claims 1 and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Singh et al. in view of Rubin et al. (Am. J. Surg. Pathol, Vol. 26, No. 3, p. 312-319, 2002) and in view of Liotta et al. (Nature reviews: Genetics, Vol. 1, p. 48-56, October 2002).

The claims are directed to a method for rank ordering characteristic signatures of cell properties, said method comprising the steps of: forming a plurality of characteristic signatures for a plurality of cell properties having been measured from a plurality of samples taken from a heterogeneous tissue region, wherein the heterogeneous tissue region includes a first portion having at least first and second types of tissue, bordered by a second portion, said second portion considered to be devoid of the second type of tissue, wherein the plurality of samples have been taken from successive locations along a determined profile of locations through the heterogeneous tissue region, with at least one sample being taken from the second portion, and wherein each of said characteristic signatures characterizing one of the plurality of properties, respectively;

providing a trend profile of cell activity for the second type of tissue along the determined profile of locations through the heterogeneous tissue region; performing statistical analysis on each of the plurality of characteristic signatures with regard to the provided trend profile; and rank ordering the plurality of characteristic signatures based on proximity to the trend profile as determined by the statistical analysis. In some embodiments, the second type of tissue comprises disease tissue. In some embodiments, a plurality of samples are taken from the first portion.

Singh et al. teach a method for rank ordering characteristic signatures of cell properties. To summarize the teaching, Singh et al. have taken normal prostate tissue that is bordered on two sides by diseased tissue and performed gene expression analysis and histological examinations of the samples resulting in a rank ordering of characteristic genes that can be used in the early diagnosis of prostate cancer.

The tissue used by Singh et al. is viewed as a heterogeneous tissue region (prostate, see figure 1 below) composed of two portions (Normal and Tumor, see figure 1 below). The first portion is composed of blood vessels and diseased tissue (Tumor) and the second portion is devoid of diseased tissue (Normal) ("Of these samples…", first paragraph, Tumor vs. normal classification, p.204). Based on a known trend for tumorous prostate to have a higher Gleason Score than normal or healthy prostate ("Gleason score", introduction, second paragraph, p. 203), Singh et al. performed histological examinations on a plurality of samples taken across the tissue to identify a characteristic signature Gleason score profile ("significant signature of GS", 3rd paragraph, Discussion, p.206). The gene models, provided in 4 and 16 gene models, of

Signh et al. provided a trend profile of cell activity for the second type (diseased) of tissue along the profile of locations in the tissue (p 204, col. 1-2). The samples were also used to perform gene expression analysis. Resulting from the gene expression analysis was a rank ordering of signature genes ("Genes were ranked...", 2nd paragraph, Results: Tumor vs. Normal classification, p. 204). In the instant case, a plurality of cell properties is interpreted to include the individual expression states of a plurality of genes, i.e. a cell property can be the expression state of a particular gene, and thus a characteristic signature is a particular profile of expression for a gene or subset of genes in the context of a particular cell or tissue type. In the course of their gene expression analysis, Singh et al. formed a plurality of characteristic signatures from a plurality of cell properties ("Type I" and "Type II", paragraph 2, Results: Prediction of Pathological features of Prostate Cancer, p. 204). Singh et al. performed statistical analysis on each of the plurality of characteristics signatures with regard to the provided trend profile. The statistical analysis was in the form of a correlation between the expression of particular genes and the Gleason score ("Correlations", Prediction of Pathological Features Of Prostate Cancer, p. 204). Singh et al. used two-step ranking procedure. In the first step, genes were ranked based on their expression relative to the tissue type (normal vs. diseased). In the second step, genes were ranked based on their correlation with the Gleason score to result in a "hierarchical clustering", interpreted as ranking ("A gene expression signature of GS...", second paragraph, Prediction of Pathological Features Of Prostate Cancer, p. 204). Singh et al. further illustrate the rank ordering of a plurality of characteristic signatures in figure 3 (p. 207).

Singh et al. do not show that a plurality of samples is taken from the first portion.

Rubin et al. shows that a plurality of samples is taken from a heterogeneous tissue region (figure 1). Rubin et al. shows an advantage of taking a plurality of samples from the first portion is that a plurality of samples increases the accuracy of the information gained from the sampling (p. 312, col. 2, abstract).

Liotta et al. shows that the molecular analysis of cells in their native tissue environment provides the most accurate picture of the *in vivo* disease state (p. 49, col. 2). Liotta et al. shows that the analysis of cells in their native tissue environment is complicated by the fact that a particular cell population of interest may constitute a tiny fraction of the total tissue population (p. 49, col. 2). In other words, the analysis of cells in their native tissue environment is complicated because tissues are heterogeneous. Liotta et al. illustrates in figure 1 the heterogeneous nature of tissues and its effect on the outcome of profiling. Liotta et al. shows that specific cell populations can be isolated from "contaminating" cellular subpopulations by microdissection (p. 50, col. 2). Liotta shows that micro dissection is easy and rapid (Box 2). Liotta et al. shows the separation yields a profile targeted to the specifically chosen population (p. 50, col. 1).

It would have been obvious to one of ordinary skill in the art to modify the method Singh et al. with the plurality of sample from the first portion of Rubin et al. because Rubin et al. successfully shows that a plurality of samples increases the accuracy of the information gained from the sampling which is an advantage. It would have been further obvious to one of ordinary skill in the art to modify the method Singh et al. in view of the plurality of sample from the first portion of Rubin et al. with the use of heterogeneous

tissues and the analysis of specific cellular populations isolated from contaminating sub-populations because Liotta et al. shows the separation yields a profile targeted to the specifically chosen population.

***Duplicate Claim Warning***

Applicant is advised that should claim 10 be found allowable, claim 37 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

***Conclusion***

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KARLHEINZ R. SKOWRONEK whose telephone number is (571)272-9047. The examiner can normally be reached on Mon-Fri 8:00am-5:00pm (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marjorie A. Moran can be reached on (571) 272-0720. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

1 May 2008

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Examiner, Art Unit 1631
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